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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/772,634	01/30/2001	Steven W. Herring	32943/KMO/A97	9937

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EXAMINER
MOHAMED, ABDEL A

ART UNIT	PAPER NUMBER
1653	8

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/772,634	HERRING ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

ACKNOWLEDGMENT OF IDS AND STATUS OF THE CLAIMS

1. The Information Disclosure Statement (IDS) and Form PTO-1449 filed 12/3/01 and 12/26/01 are acknowledged, entered and considered. Claims 1-30 are present for examination.

OBJECTION TO THE ABSTRACT, SPECIFICATION AND CLAIMS

2. The disclosure of the abstract is objected because it contain file locators "32943/KMO/A97" and "KMOPAS2606172.2*-12/8/00 2:06PM" Also, the specification and claims are objected in reciting "32943/KMO/A97" at the front corner of each page of the specification and claims. Deletion of the above file locators from the disclosure of the abstract, specification and claims would obviate this objection.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 18-21 are indefinite in the recitation "providing" because the term "providing" does not represent positive active method step.

Claims 1-3, 10-11, 16-17 and 20 are indefinite in the recitation "lyophilized protein/hydroxypropyl-α-cyclodextrin" (claims 1, 2 and 20), "protein/hydroxypropyl-α-cyclodextrin" (claim 3) and "reconstituted protein/hydroxypropyl-α-cyclodextrin" (claims 10-11 and 16-17) because it contains the use of an alternative expression wherein the limitation covers three elements, i.e., "lyophilized protein or protein or reconstituted protein" is not the same as "hydroxypropyl-α-cyclodextrin" and vise versa.

Similarly, claims 18, 19 and 21 are indefinite in the recitation "lyophilized fibrinogen/hydroxypropyl-α-cyclodextrin" (claims 18 and 21) and "lyophilized blood protein/hydroxypropyl-α-cyclodextrin" (claim 19) because it contains the use of an alternative expression wherein the limitation covers two elements, i.e., "lyophilized fibrinogen or lyophilized blood protein" is not the same as "hydroxypropyl-α-cyclodextrin" and vise versa.

Claims 3-6 are indefinite in the recitation "at least about" because it is unclear whether the narrower range defined by the "at least" or limitation is restrictive to the broader range defined by "about". It is suggested that Applicant amend the claims to recite one or the other of "at least" or, "about".

Independent claim 26 and claims dependent thereof (i.e., claims 28-30) are substantially duplicate of independent claim 22 and claims dependent thereof (i.e., claims 23-25) because claim 22 is directed to a blood protein product comprising a lyophilized solution of a stable

complex of protein and hydroxypropyl-α-cyclodextrin. Similarly, claim 26 is directed to a stabilized blood protein solution comprising a complex of the blood protein and hydroxypropyl-α-cyclodextrin. Thus, both independent claims contain products comprising a solution comprising a stable complex of protein and hydroxypropyl-α-cyclodextrin regardless whether the solution is "a lyophilized solution" or "a stabilized protein solution". Both solutions have the same components and the dependent claims have the same limitations (i.e., claims 23-25 have the same limitations as claims 28-30). As such, there would appear to be no difference in scope between claims 26, 28-30 and claims 22 -25. Hence, claims 26 and 28-30 appear to claim the same subject matter as recited in claims 22-25 (See e.g., MPEP 706.03 [k]).

CLAIM REJECTIONS-35 U.S.C. § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neurath et al., (U.S. Patent No. 4,540,573) taken with Fredholt et al., (International Journal of Pharmaceutics, Vol. 178, No. 2, pp. 223-229, 1999) or Fukunaga et al., (U.S. Patent No. 5,482,929).

The reference Neurath et al., teaches the production of a blood plasma protein-containing composition such as blood, blood plasma, blood plasma fractions including fibrinogen, etc., which is substantially free of infectious virus inactivated by a heating step which can be effected in the presence of a protein stabilizer, e.g., an agent which stabilizes labile protein against inactivation by heat. Further, the heating can be carried out using stabilizers which can tend to protect all protein particularly fibrinogen, including components of the virus, against heat if the heating is carried out for a sufficient length of time, e.g., at least 5 hours and preferably at least 10 hours at a temperature of 50^0-70^0 C, especially 60^0 C. The heat treatment can also be carried out simultaneously with alkyl phosphate treatment. The reference also teaches the lyophilization of the protein and reconstituting of the lyophilized protein (See e.g., abstract, summary of the invention, cols. 9-11 and claims 13-34).

The reference of Neurath et al., differs from claims 1-30 in not teaching specifically adding to the solution an agent such as hydroxypropyl-α-cyclodextrin (HPαCD) in an amount sufficient to from a stable complex with the protein. However, the reference motivates one of ordinary skill in the art to use various stabilizing agents to minimize potential denaturation and

aggregation of the protein by stating that it is desirable to contact the protein with the stabilizing agent of interest for a time sufficient to inactivate entirely the virus without substantial denaturation the valuable protein components therein (See e.g., col. 3, lines 45-64). Thus, suggesting the use of stabilizing agent which solubilize protein without denaturation.

Further, the secondary reference of Fredholt et al., teaches in general the use of cyclodextrins as stabilizers of proteins, and in particular HPαCD as a stabilizer of choice in an amount sufficient to stabilize drugs including peptides against both chemical and enzymatic degradation (See e.g., pages 223 and 226-227, Tables 1-3 and Figure 2). Furthermore, Fukunaga et al., teach the stabilization of polypeptides such as fibroblast growth factor (FGF) by bringing FGF into contact with aluminum salt of cyclodextrin sulfate which includes HPαCD resulted in composition which is stable under not only neutral condition but also acidic conditions in the presence of protease, and it is also stable to heat. Thus, the secondary references of Fredholt et al., or Fukunaga et al., teach methods for stabilizing protein which may include blood protein such as fibrinogen using HPαCD. Therefore, it would have been obvious to one of ordinary skill in the art to apply the teachings of the secondary references (i.e., HPαCD known to stabilize drugs including peptide and protein agents both chemical and enzymatic degradation) to the primary reference of Neurath et al., because such features are known or suggested in the art, as seen in the secondary references, and including such features into the methods of the primary reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

With respect to claims 19-21, the claims are in product-by-process format and as such, it is the novelty and patentability of the instantly claimed product that need be established and not the recited process steps, In re Brown, 173 USPQ 685 (CCPA 1972); In re Wertheim, 191 USPQ (CCPA 1976). Further, the prior art described the product as old, In re Best, 195 USPQ 430, 433 (CCPA 1977); (See MPEP 706.03 [e]). Hence, the burden of proving that the process limitation makes a different product is shifted to the Applicants, In re Fitzgerald, 205 USPQ 594.

In regard to the selection of specific temperature, duration time and the amount of HPαCD, the reference show the exemplary and preferred ranges for the temperatures, duration time and the amount of HPαCD which overlaps with the claimed ranges. Thus, in view of this, the subject formulation may be used in combination with other condition to provide a wide variety of temperature, duration of time and the amount of HPαCD or may be tailored for specific temperature, duration of time and the amount of HPαCD. Therefore, the claimed specific temperatures, duration of time and the amount of HPαCD, which fall within the scope of the prior art would have been prima facie obvious from said prior art disclosure to a person of ordinary skill in the art at the time the invention was made. Applicants claims are directed to optimization of an "art recognized variable" which is well within the purview of one of ordinary skill in the art, In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980).

Thus, the combined teachings of the prior art makes *prima facie* obvious the claimed invention's process for stabilizing a blood protein solution such as fibrinogen by adding HPαCD

and lyophilizing the solution to from a lyophilized protein/HPαCD complex thereof, absent of sufficient objective factual evidence or unexpected results to the contrary.

CONCLUSION AND FUTURE CORRESPONDENCE

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 7:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Abdel A. Mohamed

ABDEL MOHAMED
PATENT EXAMINER
GROUP 1600
TC 1600

AAM Mohamed/AAM

February 10, 2003